

## Review Article

# Pustular eruption induced by FLAG regimen in the treatment of acute myeloid leukemia: pustular eruption possibly caused by cytarabine

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**Abstract:** Background: Serious cutaneous eruptions caused by cytarabine are never reported in China. Methods: We admitted a 43-year-old man who was diagnosed with acute non-lymphocytic leukemia, and was given several chemotherapy regimens including cytarabine. And when FLAG regimens were given in the patient, the serious pustular eruption appeared. Results: After the treatment, cutaneous eruption was gradually improved. Conclusion: This case provides evidence that pustular eruption occurring in this patient during FLAG chemotherapy was probably caused by cytarabine. Clinicians in hematology departments should know morphology of serious cutaneous eruption and drugs with potential to cause cutaneous eruption in chemotherapy.

**Keywords:** Cytarabine, pustular eruption, FLAG, chemotherapy

## Introduction

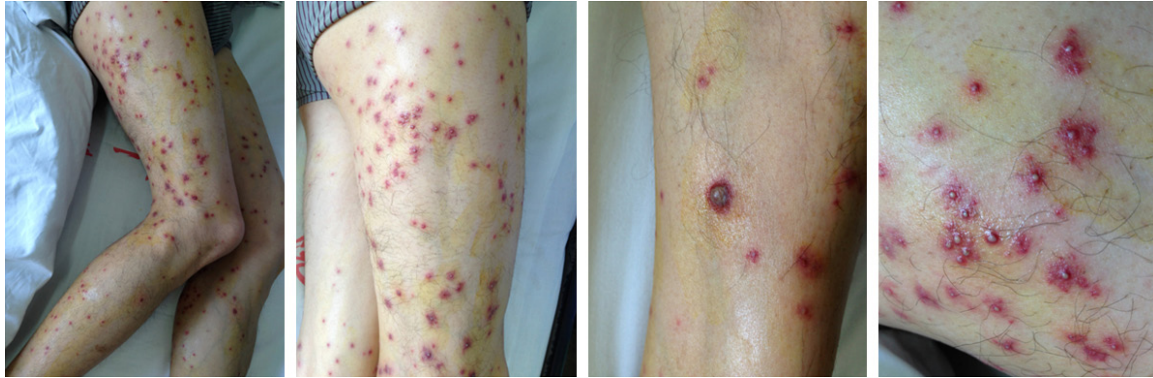
Skin reactions may occur during treatment in patients with hematological malignancies, usually as adverse reactions caused by chemotherapeutic drugs. FLAG regimen is one of the standard regimens in the treatment of relapsed/refractory acute myeloid leukemia (AML), while its component cytarabine commonly causes skin adverse reactions, mainly including skin ulcer, cutaneous eruption, pruritus and urticaria. Serious cutaneous eruptions have been reported overseas, including acute generalized exanthematous pustulosis and palmo-plantar rash. However, no such reports have been published in China. This article mainly reported one case of pustular eruption with FLAG regimen and concluded it was probably caused by cytarabine.

## Case report

A 43-year-old male patient was admitted to our hospital due to sore legs and asthenia 2 years ago. Bone marrow examination suggested: significant increase of nucleated cells, myeloblast types I and II 33.5%; POX (+), SB (+), NSE (-), NAF (-). Immunophenotyping showed: primitive/

immature myeloid cells accounted for approximately 82.86% of non-erythroid population; primitive myeloid cells accounted for 37.03%, with CD33+, CD56+ (bimodal expression), CD117+, CD34+++, CD13- and CD (HLA-DR)+++; immature granulocytes accounted for 45.83%, with CD33++, CD64+, CD56+ (partially), CD1b (bimodal expression), CD117+ (partially), CD13+, C65s++, CD (HLA-DR)+ (heterogeneous expression) and CD15+ (heterogeneous expression). Bone marrow biopsy suggested acute non-lymphocytic leukemia. Karyotype analysis showed 45, X, -Y, t(8;21)(q22;q22). Diagnosis of "acute myeloid leukemia (M2a)" was confirmed. Since January 30, 2012, the patient had been successively treated with AA, IA, IA, medium-dose Ara-C, HAA and HA chemotherapy regimens. During chemotherapy with medium-dose Ara-C regimen, the patient developed cutaneous eruptions primarily on abdominal skin, which were pinpoint-like, not higher than skin surface, accompanied by pruritus and spontaneously resolved. Subsequently, same cutaneous eruptions recurred during chemotherapy with HAA and HA regimens, and resolved after external application of Bactroban ointment.

## Pustular eruption reduced by FLAG regimen



**Figure 1.** The patient developed pustular eruption in the fourth day of chemotherapy.

On June 27, 2013, the patient was hospitalized again due to relapse and received chemotherapy with FLAG regimen (rhG-CSF 300 ug every day suggested: significant increase of nucleated cells, myeloblast types I and routine blood test showed: white blood cell  $2.2 \times 10^9/L$ , neutrophil  $0.9 \times 10^9/L$ , hemoglobin 116 g/L and platelet  $67 \times 10^9/L$ ). On June 29, 2013 (Day 3 of chemotherapy), the patient developed a few cutaneous eruptions, primarily on abdomen, which were pinpoint-like, without significant pruritus and of the same nature as previous. Allergy to Ara-C was suspected. Zyrtec 10 mg qn was used for anti-allergic treatment. However, cutaneous eruptions were not significantly improved. On July 1 (Day 4 of chemotherapy), the patient suddenly developed pustular eruption (as shown in the **Figure 1**), beginning from the abdomen and gradually spread to lower limbs and upper limbs, accompanied by pruritus. Blood routine on July 1 showed: white blood cell  $2.5 \times 10^9/L$ , neutrophil  $2.413 \times 10^9/L$ , hemoglobin 107 g/L and platelet  $33 \times 10^9/L$ . It was considered that further chemotherapy might cause bone marrow depression and aggravate infection. So chemotherapy was discontinued. The patient received Vancocin 0.5 q8h for anti-infective treatment. Dermatology consultation was performed. Drug eruption and folliculitis were considered. Bactroban and iodophor for external use were applied. Skin biopsy was performed. Skin pathological examination suggested: mild basket-like epidermal hyperkeratosis with follicular keratotic plugging, and focal epidermal spongiosis with reticular degeneration and mild neutrophil infiltration. Papillary layer of dermis showed focal degeneration, with local infiltration of neutrophils, nuclear dusts and a few mononuclear

inflammatory cells. Extravascular red blood cells were observed. In conjunction with clinical observations, drug eruption was first considered. Blood routine on July 4 showed: white blood cell  $0.6 \times 10^9/L$ , neutrophil  $0.4 \times 10^9/L$ , hemoglobin 98 g/L and platelet  $22 \times 10^9/L$ . Liver and renal functions showed no significant abnormality. CRP: 6.2 mg/L (normal range: 0-8). Erythrocyte sedimentation rate: 26 (normal range: 1-15). The patient again received subcutaneous injection of rhG-CSF 150 ug every 12 hours and folliculitis was gradually improved. Body temperature gradually returned to normal.

### Discussion

FLAG regimen is considered as a relatively effective consolidation chemotherapy regimen in the treatment of refractory/relapsed AML (except M3) with few side effects [1], cutaneous eruption caused by which has not been reported. FLAG regimen consists of cytarabine, fludarabine and granulocyte colony-stimulating factor (G-CSF). Reports of cutaneous eruption caused by cytarabine are relatively common, while cutaneous eruption caused by G-CSF or fludarabine is rarely reported.

Cytarabine is mainly used to induce remission and as maintenance therapy in adult and pediatric acute leukemia. It is one of the most effective drugs in the clinical treatment of AML. During chemotherapy, it may cause adverse reactions in various systems, including bone marrow depression, various serious infections, cytarabine syndrome, neurotoxicity and conjunctivitis. Adverse skin reactions mainly include skin ulcer, alopecia, pigmented spot, cutaneous eruption, pruritus and urticaria. For

cutaneous eruption suddenly occurring during chemotherapy in patients with hematological malignancies, primary disease, various infections and drug hypersensitivity should be considered. Drug hypersensitivity is a type of rare but life-threatening systemic hypersensitivity, particularly in patients entering bone marrow depression phase after chemotherapy, where the outcome may be fatal. It often occurs after use of certain drugs, e.g. sedative hypnotic drugs, for 3-6 weeks, manifested as cutaneous eruption, fever, hepatic and renal impairment and increased eosinophil, requiring timely hormone therapy. Suzuki HI et al. reported 2 cases of acute hypersensitivity after IA (cytarabine + idarubicin) chemotherapy and relevant mechanism [2].

Pustular eruption may be induced by primary disease. Akasaka H [3] et al. reported a case of palmoplantar pustulosis due to relapse, which resolved after CR was achieved with bone marrow transplantation. In this patient, skin biopsy did not suggest tumor cell infiltration.

However, most cutaneous eruptions caused by cytarabine, even including those with serious morphology and behavior, can resolve after symptomatic supportive therapy, generally with good prognosis. As reported in the New England Journal of Medicine, in a 52-year-old initially treated male AML patient, bone marrow examination did not suggest remission after standard IA regimen, and medium-dose cytarabine (1500 mg/m<sup>2</sup>) q12h marrow examination did not suggest remission after standard dose was administered, the patient developed palmoplantar rash, including large areas of erythema and blisters on palms and soles. After symptomatic supportive therapy, the patient completed chemotherapy and cutaneous eruption resolved 20 days after chemotherapy [4]. Selin Ayta reported, the patient developed palmoplantar rash, including large areas of erythema and blisters on acromelic with bullae formation during treatment with mitoxantrone plus cytarabine, which spontaneously resolved within 2 weeks without any treatment [5].

Tuyet A. Nguyen et al. reported a 40-year-old female patient transforming from MDS to AML who developed fever and miliaria-like rash in bone marrow depression phase after IA chemotherapy. However, it was considered to be possibly caused by neutropenic fever and idarubicin [6].

Annie Chiu also reported a 14-year-old female patient with CD30+ large cell lymphoma who received the 2<sup>nd</sup> cycle of chemotherapy with high-dose MTX plus cytarabine. Within the first 24 h of chemotherapy, the patient developed generalized, diffuse, painful, pruritic pustular eruption, which disappeared within 4 days. Through separate administration of MTX and cytarabine, it was confirmed that previous eruption was caused by cytarabine [7].

Fludarabine may also cause cutaneous eruption, but this is extremely rare. Among 29 patients receiving fludarabine based chemotherapy, only 1 patient developed diffuse cutaneous eruption [8].

G-CSF can also induce bullous pyoderma [9]. However, the patient did not develop similar eruption after previous treatment with G-CSF and cutaneous eruption was continued to be improved under subsequent use of G-CSF in bone marrow depression phase. Therefore, cutaneous eruption caused by G-CSF was considered impossible.

In conclusion, the authors considered that pustular eruption occurring in this patient during FLAG chemotherapy was probably caused by cytarabine. However, involvement of fludarabine could not be completely excluded. Clinicians in hematology departments should know morphology of serious cutaneous eruption and drugs with potential to cause cutaneous eruption in chemotherapy, so as to give timely and correct treatment during chemotherapy.

### Disclosure of conflict of interest

None.

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## Pustular eruption reduced by FLAG regimen

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